Acidophil stem-cell pituitary adenoma in a prepubescent female

Case report

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Acidophil stem-cell pituitary adenomas account for less than 5% of pituitary tumors. Only 15 cases have previously been reported, with a mean age of occurrence of 38.7 years. A case of this unusual tumor is reported in a prepubertal girl. Clinical symptoms included prominent behavioral disturbance with associated headache and visual disturbance. There was marked elevation of serum growth hormone concentration without clinical features of growth hormone excess, suggesting that this tumor has the capacity to excrete biologically inactive hormones. The clinical and pathological features of this unusual invasive pituitary tumor are reviewed; the age spectrum for this neoplasm must be expanded to include prepubertal children.

KEY WORDS • pituitary adenoma • acidophilic stem cell

Acidophil stem-cell adenomas are relatively rare, constituting 3% to 5% of all pituitary tumors. Reported patients with this neoplasm have ranged in age from 17 to 60 years, with only two patients being under 20 years of age. The mean age for males and females is 46.2 and 33.8 years, respectively. A case of an acidophil stem-cell tumor is described in a prepubertal girl, a previously unreported occurrence.

Case Report

This previously healthy girl was hospitalized at 11 years of age for psychiatric evaluation of behavioral regression characterized by unprovoked crying, increased need for attention, and decreased appetite. Headaches of varying intensity had been present for 6 months, and she had complained of photophobia and a progressive decrease in visual acuity. Her medical history was significant for secondary enuresis beginning at the age of 6 years despite being toilet trained at 2 years of age. Available growth parameters indicated growth of normal velocity along the 75th percentile. In school, she had repeated third grade and had been placed in learning disability classes for mathematics.

Examination. General physical examination revealed Tanner I development of breasts and genitalia; no galactorrhea could be elicited. She was uncooperative and had marked emotional lability, making reliable ophthalmological assessment difficult. Best corrected visual acuity was 20/200 in each eye. Pupils were 4 mm and symmetrically responsive to light, with no afferent pupillary defect. Confrontation visual fields were inconsistent, but demonstrated tunnel fields at two test distances, suggestive of a functional component. There was a tendency in each eye to respond more consistently nasally than temporally. Color vision was absent. Extraocular motility, muscle balance, slit lamp, and funduscopic examinations were normal. The remainder of the neurological examination was normal.

Cranial computerized tomography scans demonstrated a high-density mass arising from the suprasellar region (Fig. 1). Magnetic resonance (MR) imaging showed the mass (measuring 5.1 × 4.1 cm) to be isoointense to low intensity on T1-weighted images, with slightly increased intensity on both proton density and T2-weighted sequences (Fig. 1). Preoperative hormonal evaluation was significant for a markedly elevated unstimulated growth hormone (GH) level of 243
Acidophil stem-cell pituitary adenoma

FIG. 1. Neuroimaging studies. Upper Left: Computerized tomography scan demonstrating a high-density circumscribed mass filling the third ventricle. Upper Right: Sagittal T₁-weighted magnetic resonance (MR) imaging showing the mass to be relatively isointense with the surrounding brain. There is compression of the optic chiasm and moderate hydrocephalus. Lower: On the axial balanced proton density (left) and T₂-weighted (right) MR images the mass is predominantly of high signal intensity.

ng/ml (normal < 10 ng/ml) that was not altered by clonidine stimulation. Somatomedin-C, or insulin-like growth factor I, was elevated at 4.3 U/ml (normal < 1.4 U/ml). Free thyroxine and thyroid-stimulating hormone levels were in the normal range; prolactin concentration ranged from 16.9 to 21.0 ng/ml (normal < 20 ng/ml). Findings of a normal serum sodium concentration and urinary concentrating ability (specific gravity to 1.036) excluded diabetes insipidus. At a chronological age of 9 years 3 months the patient's bone age was 8 years 6 months. Neuropsychological evaluation, including the Halstead-Reitan Neuropsychological Battery, demonstrated pronounced difficulties with abstract reasoning, problem-solving, sequencing, and mental flexibility. She had bilateral deficits in fine motor speed, agility, and strength. Difficulties with tactile sensation and stereognosis were improved when she used both hands simultaneously. There was evidence of diffuse cerebral dysfunction, manifested by language dyspraxias, dysgraphia, dyslexia, dysarthria, dyscalculia, and visual-letter dysgnosia.

Operation. Surgery for removal of this tumor, which filled the third ventricular space, was through a right frontal craniotomy and transcallosal approach. A 2-cm incision was made in the midline of the corpus callosum at the level of the coronal suture of the skull. After the internal cerebral veins were visualized, a very tough reddish-brown capsule filling the entire third ventricle was encountered. Sharp dissection was required to open it. The tumor was soft and very vascular, without evidence of cyst formation. Subtotal resection was accomplished with suction and cautery down to the preoptic cistern, 5 cm below the inferior edge of the corpus callosum. The remainder of the tumor was adherent to the ventricular walls and could not be removed safely.

Postoperative Course. The patient was somnolent for a few days but recovered to her premorbid neurological state. In the immediate postoperative period, diabetes insipidus was noted and therapy was begun with 1-desamino-8-D-arginine vasopressin (DDAVP). Repeat neuropsychological evaluation 2 weeks postoperatively revealed a significant overall improvement in her level of functioning. Tactile sensation of her hands was unchanged, except that there was now a deterioration in performance when both hands were used simultaneously. No regression of the remaining tumor was noted with a brief trial of bromocriptine therapy. She subsequently received cranial irradiation, 4950 Gy delivered in 35 treatments over 52 days.

Six months following craniotomy the patient was hospitalized because of persistent headaches associated with nausea and vomiting. At that time she was found to have a large cystic component arising from the superior aspect of the tumor within the third ventricle. An Ommaya reservoir was placed with the tip inserted into the tumor cyst, and dark, bloody fluid was aspirated. This resulted in clinical improvement, but the Ommaya reservoir required revision 1 month later due to the recurrence of headaches and evidence of cyst regrowth on MR imaging. At that time, the serum prolactin concentration was elevated at 43.9 ng/ml (normal < 20 ng/ml).

One year postoperatively, the tumor size remains stable. Despite the presence of optic atrophy, the patient's best corrected visual acuity has improved to 20/40 in the right eye, while the left remains deficient at 20/400, with an afferent pupillary defect. Extraocular motility has remained normal; however, she has 25 prism diopters of intermittent exotropia on the left, believed to be sensory in origin. Her diabetes insipidus continues to be treated with DDAVP. Serum GH concentrations are decreased from pretreatment levels, but remain elevated at 39.4 ng/ml. These levels are still not stimulated by clonidine or suppressed by glucose infusion. Growth has remained consistent between the 75th and 90th percentiles. At a chronological age of 12 years 7 months, the patient's bone age is 11 years, within the normal limits of variability. Thyroid replacement has also been required. Prolactin concentrations which had peaked at 43.9 ng/ml 6 months after surgery, had returned to the normal range (13.4 ng/ml) by 1 year.
Neuropsychological evaluation reveals an estimated intelligence quotient of 98, with deficits in mathematics and overall knowledge. There was significant overall improvement in all areas of cerebral functioning, although she was still functioning in the mildly impaired range. Her fine motor dexterity remains moderately impaired, with progression of the previously noted deficit when both hands were used.

**Histopathological Findings.** Microscopically, the tumor consisted of sheets of relatively monomorphous polygonal cells with abundant cytoplasm. The normal fine reticular network of the pituitary was markedly expanded around the sheets of cells. The tumor nuclei were round to oval, with fine to coarsely granular chromatin and strikingly prominent nucleoli. Sparse mitotic figures were seen. Immunohistochemical staining with antibodies directed against GH and prolactin revealed scattered positive cells (Fig. 2). Stains for adrenocorticotropic hormone, luteinizing hormone, the alpha subunit, keratin, alpha-1 antitrypsin, human chorionic gonadotropin, alpha-fetoprotein, S-100 protein, and glial fibrillary acidic protein did not reveal any immunoreactivity. Electron microscopy showed cells containing numerous bizarre pleomorphic mitochondria, abundant (often stacked) smooth endoplasmic reticulum, and a few small (50- to 150-nm) secretory granules, consistent with prolactin granules (Fig. 3).²

**Discussion**

Acidophil stem-cell pituitary adenomas are rapidly growing tumors considered to represent an incompletely differentiated neoplasm arising from the common precursor of GH- and prolactin-secreting cells. Even though the existence of an acidophilic stem cell was first postulated by Furth and Clifton in 1966,¹ neoplastic proliferation of such a cell was not actually identified until 10 years later by Horvath, et al.⁴ The tumor is generally chromophobic, but with varying degrees of acidophilic staining due to an abundance of bizarre mitochondria and accumulation of smooth en-

![Fig. 2. Photomicrographs showing the histopathology of the pituitary tumor. Upper Left: There are sheets of monomorphous, polygonal tumor cells of pituitary origin. The nuclei are hyperchromatic, and nucleoli are prominent. H & E, × 400. Upper Right: Mitotic figures are present. PAS stain, × 400. Lower Left: There is expansion of the normally fine reticular network. Reticulin stain, × 100. Lower Right: Cells staining with antibodies for prolactin (left) or growth hormone (right) are seen. PAP immunocytochemistry staining, × 400.](image-url)
Acidophil stem-cell pituitary adenoma

doplasmic reticulum. As in all previously reported cases, prolactin was identifiable in the tumor of the present patient; GH, present in most cases, was also detected in this patient. Electron microscopy typically reveals the mitochondrial abnormalities which are characteristic of these tumors, including oncocytic transformation, focal cavitation, and mitochondrial gigantism.

In the only clinically detailed series of reported patients with acidophil stem-cell adenomas, Horvath, et al.,\textsuperscript{3,4} outlined the clinical and histological characteristics of this uncommon tumor (Table 1). Among their series of 15 patients (nine females and six males), only two were under 20 years of age and none were prepubertal. The most common presenting complaint was headache, in two males and five females. Behavioral alteration or psychological complaints (including anxiety, depression, and decreased libido), loss of visual acuity, and visual field defects were each seen in four males and one female. All three of these features were evident in our patient and, although with treatment there has been improvement in her visual function, marked behavioral problems, chronic headaches, and

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* Summary of data reported by Horvath, et al.,\textsuperscript{3,4} with the addition of the present case (Case 16). Behavior changes included decreased libido or depression.

**TABLE 1**

Clinical features of 16 reported patients with acidophil stem-cell pituitary adenomas *

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**FIG. 3.** Ultrastructural study of pituitary tumor. Electron micrographs revealing the presence of prolactin granules, abundant endoplasmic reticulum (left), and the bizarre pleomorphic mitochondria (right) which are the hallmark of the acidophil stem-cell adenoma. × 4400 (left) and × 17,700 (right).
sleep disturbance have persisted. Acromegalic features were noted in three of the reported patients (two males and one female). Despite extremely high levels of GH, our patient had no clinical or radiographic features of GH excess. This suggests that the GH being secreted by the tumor was biologically inactive, despite appropriate receptor binding in an in vitro assay. Eight of the nine reported females had galactorrhea and menstrual abnormalities. One year after completion of radiation therapy, our patient (now 13 years of age and on replacement therapy for hypopituitarism) has undergone thelarche and adrenarche, although menses have not yet begun.

In a recent series from the Mayo Clinic, 74% of pituitary tumors which secreted both GH and prolactin were macroadenomas, of which approximately one-third were invasive. Although such tumors more commonly invaded inferiorly into the sphenoid sinuses, in our patient the majority of extrasellar expansion was superiorly, with resultant chiasmal compression and bone destruction of the sella turcica.

Because they are uncommon, little clinical information is currently available regarding the long-term outcome following treatment of this particular tumor; however, the volume of the tumor mass and its tendency toward invasion suggest a relatively poor prognosis. One year after subtotal resection and radiation therapy, our patient's clinical examination and tumor size have remained stable.

Acidophil stem-cell pituitary adenomas are uncommon tumors, previously described only in older adolescents and adults. Our case now expands the age spectrum to include prepubertal children. Electron microcopy is necessary to confirm the diagnosis, revealing the striking mitochondrial abnormalities and accumulated endoplasmic reticulum necessary to distinguish this tumor from the well-differentiated mixed GH- and prolactin-secreting adenoma.

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References


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